

Jörg Gromoll, Christian Schiffer and Frank Tüttelmann

Leave No Man Behind



The burden of involuntary childlessness, carried by millions of couples worldwide, is caused by either male or female infertility. However, for traditional and social reasons research on male reproductive health was neglected for a long time. Now the “forgotten man” experiences his well-deserved renaissance.

Micromanipulation of germ cells: Cultivated human stem cells, spermatogonia (the precursors of spermatozoa), are isolated with a pipette and then examined.

Reproduction has driven our species' success since its origins as a staunch guard against evolutionary standstill. The complexity of genetic, endocrine, and cellular processes that the term "reproduction" summarises is amazing. Success depends on all of them to work as an entity: Only one weak link in a long chain of events – and a couple will not be able to conceive.

The likelihood that a couple remains involuntarily childless depends on various factors – above all, age. As people set aside longer periods of time for education and career development, the desire to have children is often delayed to a later phase of life. Yet the time

window for reproduction is narrow: Opening with puberty and closing again long before the onset of the female menopause, only twenty to twenty-five years remain to conceive.

Early adverse effects on fertility and the health of offspring begin to manifest already between 35 and 40 years. For example, already mild hormonal dysbalances frequently associated with age can disrupt the maturation of germ cells and, therefore, hamper fertilisation. In men, spermatogenesis becomes increasingly inefficient over lifetime, while for women the risk of genetic diseases like Down syndrome on offspring increases.

Physicians and researchers have been working for a long time to help couples fulfil their desire to have a child in spite of infertility. The breakthrough came in 1974 when British physiologist Robert Edwards succeeded in creating the first "test-tube baby" by fusing sperm and egg cells in vitro. His in-vitro fertilisation (IVF) technique won Edwards the Nobel Prize in medicine in 2010.

Technologies significantly evolved since then: While IVF still employs millions of sperm to fertilise one egg, intracytoplasmic sperm injection (ICSI) – at least in theory – requires only one single sperm to be injected into each oocyte. To

Motility analysis of human sperm. A singular sperm, head-tethered to a microscope slide, is recorded with a fast camera to provide visual data for mathematical reconstruction and analysis of the flagellar beating pattern.

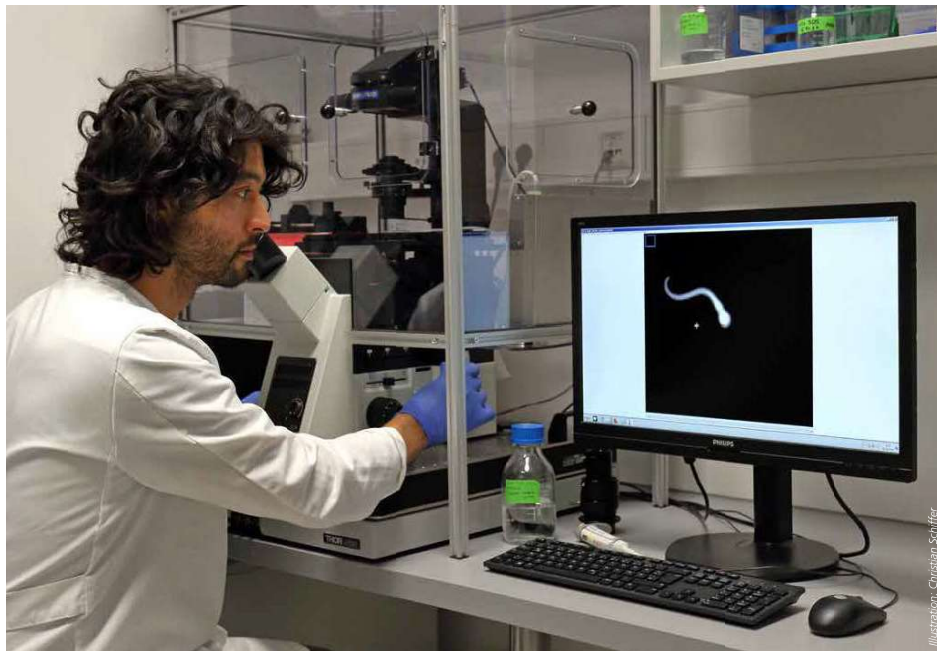


Illustration: Christian Schiffer

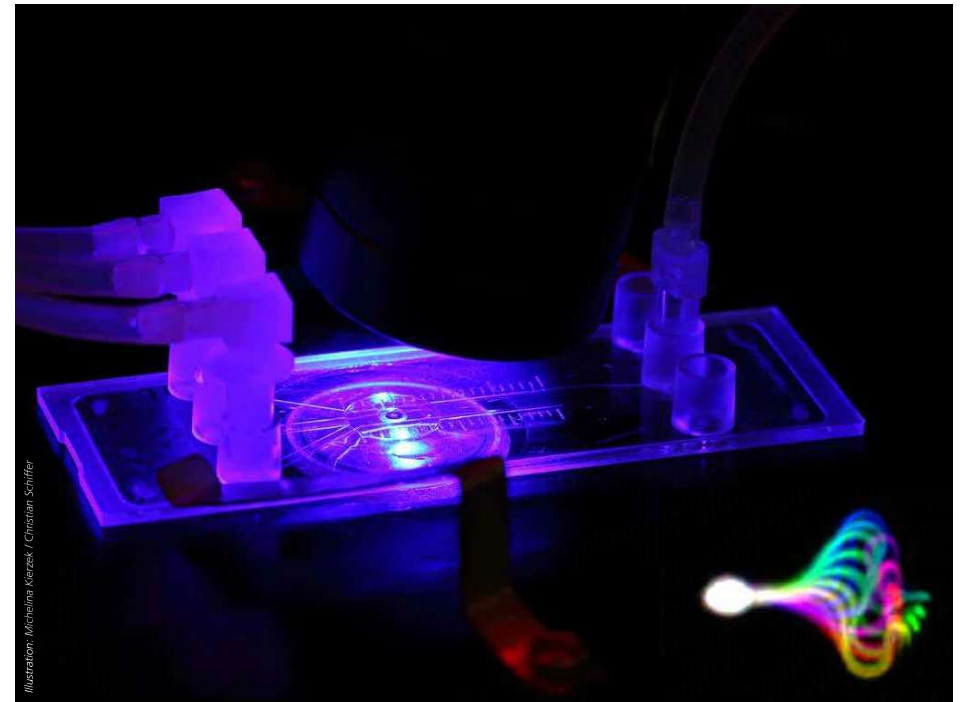


Illustration: Michaela Kierzel / Christian Schiffer

To understand navigation of freely moving sperm, they are observed under the microscope inside shallow glass capillaries with a high-speed camera. A sequence of successive, aligned, superimposed, and color-coded images allows the flagellar beating pattern to be visualised (bottom right).

many thousands of involuntarily childless couples every year, IVF and ICSI offer the alternative to resignation.

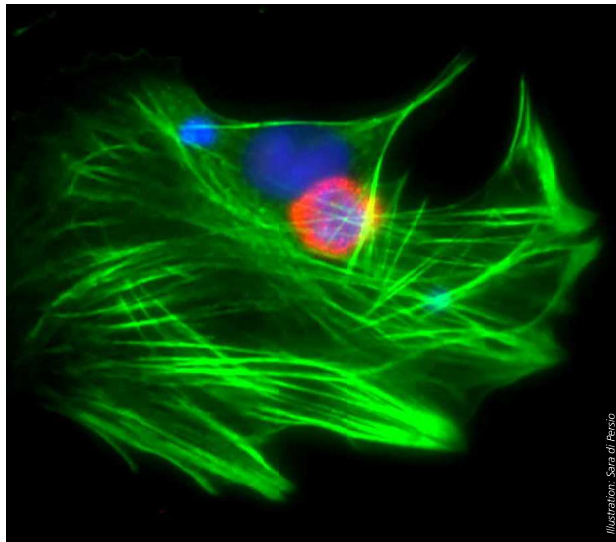
Indeed, reproductive medicine is in fact so successful that in some countries it is affecting demographic trends. In Denmark and Germany, 8 percent and 4 percent, respectively, of all newborns are conceived through assisted reproduction – with a marked upward trend in both countries. According to the most recent projections, by the end of the century around 300 million humans will owe their life

to assisted reproduction worldwide.

However, the insights into the underlying pathophysiology and attempts to cure infertility are not equally distributed between the sexes. Traditionally, mostly women were blamed for infertility in relationships – mainly because scarcely anything was known about the formation of male germ cells and the many stages at which spermatogenesis can fail. Basic science on male reproduction, crucial to understand male (in-)

fertility, was therefore seriously neglected.

Only in recent decades it has become clear that the causes of involuntary childlessness are in fact distributed equally between the sexes: in around 30 percent of cases, male infertility is to blame, and in another 30 percent, the origin lies with the woman. In 20 percent of cases both partners have a fertility problem, and for the remaining 20 percent of couples, current diagnostic tools fail to unravel the origin of infertility. But realising that the male contri-



Immunofluorescence staining for a germ cell (red) between somatic cells (green).

What is the reason for this paradigm shift? A growing body of evidence suggests that male reproductive functions are not only relevant to fatherhood, but also affect overall health and wellbeing – both in the man himself and in his children. Male infertility has to be understood as only one symptom of a complex disease.

The situation with respect to children conceived through assisted reproduction is also complex. In-vitro fertilisation means to circumvent any natural selection in the female genital tract. It would appear that this is not without its consequences: a child conceived through assisted reproduction is at a higher risk of below-average birth weight and seemingly more prone to other comorbidities. A Belgian team led by Herman Tournaye recently dem-

onstrated that, through IVF and ICSI, infertile men can transmit impaired spermatogenesis to their male offspring.

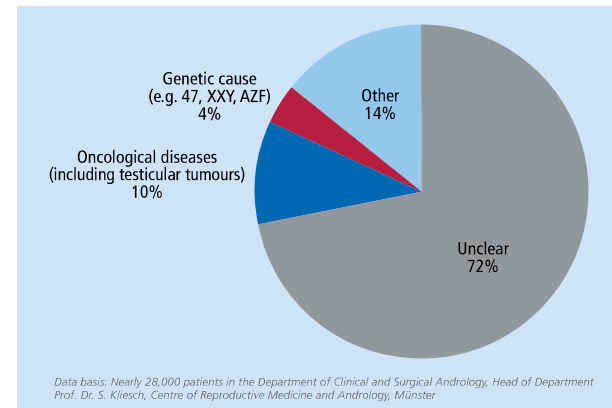
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The aim of reproductive medicine is to help couples fulfil their desire to have a child. But help is not yet available for everyone.

Illustration: Fotolia



Data basis: Nearly 28,000 patients in the Department of Clinical and Surgical Andrology, Head of Department Prof. Dr. S. Kliesch, Centre of Reproductive Medicine and Andrology, Münster

What causes male infertility? A clear reason can only be identified in about 30 percent of men only, with around 4 percent of cases being due to genetic factors; in over 70 percent of cases the causes are "unexplained".

egies to enable infertile patients to conceive even without in vitro fertilisation. "Assisted natural reproduction" – this is how we envisage the next generation of reproductive medicine. There may be many routes to achieve this goal, but one thing we know for certain: Men must not be left behind.

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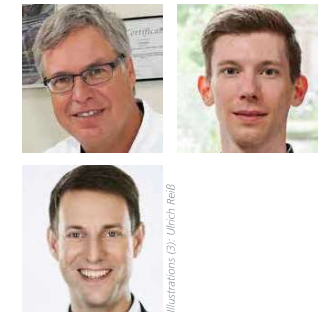
Understanding these unforeseen consequences of artificial intervention in human reproduction has just begun. The introduction of IVF and ICSI has launched a cross-generational long-term experiment whose results only future generations will be able to evaluate.

Research to overcome our lack in understanding male reproductive health is both a scientific and a medical imperative. To tackle this task, we have set up a DFG funded Clinical Research Unit in Münster. The interdisciplinary Unit provides the framework for clinicians and researchers in genetics, biology, and bioinformatics to work on the causes, diagnosis, and treatment of male infertility. Currently, around 70 percent of male patients leave the diagnostic process described as "unexplained infertility". By using innovative methods such as whole genome and methylome

sequencing and novel sperm tests, we aim to slash this number over the coming years.

The Research Unit's work programme also takes into account the complex disorders that can affect male reproductive biology beyond infertility. As a model, we collaborate with the Department of General Paediatrics of our University Hospital to study primary ciliary dyskinesia (PCD). This is a rare congenital disease involving defects in the action of the cilia lining the respiratory tract. The cilium is the link: The flagellum that propels a sperm cell shares its molecular architecture with the cilia in the respiratory tract. Genetic factors that cause PCD can therefore also result in poor sperm motility and cause male infertility.

Our Research Unit also pursues concepts that go far beyond the scientific study of male reproductive health and development of innovative diagnostic tools. For example, teams are working on hormonal intervention strategies to stimulate spermatogenesis in infertile men. We foresee such strat-



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